Hydrolytic reactions in the presence of water-soluble hydrophobic polyacids.

Jager, Jan

SUMMARY

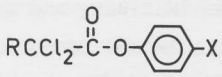
Poly(methacrylic acid) (PMAA) is a synthetic, water-soluble poly-(carboxylic acid), containing hydrophobic methyl side-chains. In aqueous solution, at low degrees of ionization, PMAA resides in a compact-coil conformation characterized by the presence of hydrophobic microdomains. At present, there is no consensus about the exact origin and relative contributions of the factors responsible for the stabilization of the compact-coil conformation. Both intramolecular hydrophobic interactions and London dispersion interactions between the methyl side-chains are believed to play an important role. At a critical degree of ionization, PMAA undergoes a conformational transition to an extended, random-coil conformation. There is considerable interest in the properties of PMAA in dilute aqueous solutions since the conformational transition within PMAA to some degree mimics the helix-coil transition shown by many proteins. The present work originates primarily from our interest in the influence of medium effects on hydrolytic reactions. Therefore, we have investigated the effect of hydrophobic poly(carboxylic acid)s on rates and thermodynamic activation parameters of hydrolytic reactions in order to attain a deeper insight into the structural properties and features of these polymers in aqueous solution. Special attention has been paid to the conformational properties of PMAA.

In Chapter 1 a survey of the relevant literature is given concerning the conformational properties of hydrophobic polyacids, with special emphasis on PMAA. The experimental techniques which can be applied to probe the conformational transition of PMAA are briefly reviewed.

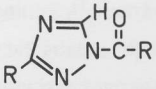
The effect of changes in the hydrophobic side-chain of poly(carboxylic acid)s on the conformational behavior is examined in Chapter 2. Potentiometric titration curves of poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), and poly(ethacrylic acid) (PEA) were analyzed in terms of successive ionization constants of a suitably sized subunit of the polymer chain. PAA, which lacks a hydrophobic side-chain, exhibits no conformational transition upon ionization. By contrast, both PMAA and PEA are characterized by a bimodal population distribution. The confor-

mational transition in PEA is more pronounced than that in PMAA, most likely as a result of the increased hydrophobicity of the side-chain compared to that of PMAA.

In Chapter 3 it is demonstrated that kinetic probes can provide detailed information about the conformational state of hydrophobic poly(carboxylic acid)s. In aqueous solutions of unneutralized PMAA, the neutral (*i.e.* water-catalyzed) hydrolysis of acyl-activated esters (1) and 1-acyl-1,2,4-triazoles (2) is strongly retarded. Rates and thermodynamic



1



2

activation parameters have been interpreted in terms of effective binding of the hydrophobic substrates to hydrophobic microdomains within the PMAA hypercoil. The disappearance of the rate inhibition above pH *ca.* 5 is ascribed to the pH-induced conformational transition of PMAA from a compact coil to a random coil. Only small rate retardations were found in the presence of PAA, poly(methacrylamide), poly(N-vinylpyrrolidone), and low molecular weight additives (methacrylic acid and isobutyric acid). In the presence of PMAA, the enthalpy and entropy of activation undergo large and partly compensatory changes, the rate retardations being dominated by the increase in the enthalpy of activation. This behavior is rationalized by assuming decreased hydration of the dipolar transition state for hydrolysis in hydrophobic microdomains. However, it is noted that the activation parameters also reflect the temperature dependence of the hydrophobic binding process.

Instead of changing the hydrophobicity of the apolar side-chain of poly(carboxylic acid)s, the conformational properties can also be varied by changing the hydrophobic-hydrophilic balance within the polymer coil. This approach is exemplified in Chapter 4, where the conformational properties of a series of random acrylic acid-methacrylic acid (AA-MAA) copolymers are described. Potentiometric titrations, solubility experiments employing the water-insoluble dye Orange OT, spectroscopic studies using the cationic probe ethidium bromide, and, finally, kinetic studies of the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole all indi-

cate that unneutralized AA-MAA copolymers only exhibit a conformational transition when the methacrylic acid content exceeds *ca.* 55 mole %. In addition, a water-soluble copolymer containing chiral hydrophobic side-chains (copoly(acrylic acid-1-menthyl acrylate)) has been synthesized Preliminary results indicate, that at low degrees of ionization this copolymer resides in a (chiral) condensed phase. However, further investigations (*i.e.* by using a *chiral* kinetic probe) will be necessary in the future.

In the final chapter (Chapter 5), the influence of protein denaturants (such as alcohols, urea and urea derivatives, and quaternary ammonium salts) on the stability of the compact-coil conformation of PMAA is described. These protein denaturants, when added to aqueous solutions of PMAA, reduce the rate retardation of the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole considerably. The effect is ascribed to a destabilization of the compact-coil conformation. These results, together with spectroscopic measurements using ethidium bromide provide further insight into the denaturing ability of protein denaturants. Interestingly, the trends in denaturing effectiveness of the protein denaturants toward unneutralized PMAA are in remarkable agreement with those for the denaturation of biopolymers. It is found that the denaturing ability increases with increasing hydrocarbon content and alkyl substitution:

n-butanol > *t*-butanol > *n*-propanol > ethanol > methanol

N,N,N',N'-tetramethylurea > N,N'-dimethyl urea > N-methylurea > urea